Zn2+ Ions-Induced Immune Pediatric Anti-Respiratory, Anti-Pulmonary, and Anti-Thrombotic Activities During ROS Generation Against Severe COVID-19 Infection, and its Zn2+-Binding Proteins Molecular Mechanism

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Zinc-induced pediatric immune intake; 2019-CoV prevention; COVID-19 bronchitis and pneumonia; Anti-thrombus formation; Zn2+ ions-coordinated pattern

1. Abstract
Zinc induced pediatric preventing respiratory 2019-nCoV is required that supplementation with zinc gluconate 20 mg in Zn deficient children resulted in a nearly twofold reduction of acute lower respiratory infections as well as the time to recovery. Zinc supplementation in children is associated with a reduction in the incidence and prevalence of pneumonia. Preventing 2019-nCoV pneumonia is required that zinc supplementation alone (10 to 20 mg) for more than 3 months significantly reduces in the rate of pneumonia. Zinc gluconate supplement may result in significant reduction in respiratory morbidity among children with acute lower respiratory infections. Treatment with 20 mg zinc/day accelerates recovery from severe pneumonia in children.

Zn2+-induced pediatric anti-respiratory activity is enhanced and provided direct protective effects with using zinc gluconate 10 mg, zinc supplementation 30 mg/day, and zinc 15 mg~30 mg daily with lozenges. Zn2+ -induced pediatric anti-pulmonary activity is enhanced for 20 mg zinc/day as adjuvant, 30 mg/day of zinc supplementation with CKD.

Zn2+-induced pediatric anti-thrombotic activity is enhanced that zinc ions could modulate coagulopathy by hypercoagulation and the microangiopathy, Zn2+ induced platelet-dependent fibrin formation lead to modulation of thrombus formation, and Zn2+-induced platelet activation enhances anti-thrombus growth. The thrombosis of the coagulopathy by hypercoagulation and the microangiopathy may be anticipated to be inhibited by zinc ions that zinc (10-20 mg daily) could modulate hypercoagulation and subsequent COVID-19 thrombus formation.

Zinc induced immune pediatric intakes are required to be effective range 10~20 mg/d for 2019-CoV prevention, 10~30 mg/d for reduction of COVID-19 bronchitis, 20~30 mg/d for recovery from COVID-19 pneumonia, and zinc 10~30 mg/d for anti-thrombus formation and growth and are required 3 mg/day for 7 month to 3 years, 5 mg/day for 4~ 8 years, and 8 mg/day for 9~13 years in
children. Zinc supplementation have been assessed, from 15 mg to 140 mg/week, with the upper range exceeding the Recommended Daily Infection (RDI) for children of 2 mg/day for children less than one year of age and up to 7 mg/day for children between 1 to 3 years.

Zinc induced Reactive Oxygen Species (ROS) generation and oxidative stress in COVID-19 bronchitis, pneumonia and thrombosis in children that are caused by mRNA degradation and oxidative respiratory burst, and thrombosis revoluted by tissue damage and ROS resolve venous thrombus. By rapid ROS production, the oxidative stress in pediatric diseases causes an oxidative and a respiratory burst.

Thus, Zinc(II) ions-induced immune antiviral and antithrombotic molecular mechanisms may be caused that Zn2+ ions are bound with COVID-19 surface proteins molecules, such as S (spike), E (envelope), M (membrane) and N (nucleocapsid) proteins and with coagulated thrombus protein by Zn2+ ion-triag bindings tetrahedrally or Zn2+ triad binding structure formation.

2. Introduction

Epidemiological and clinical characteristics for rapid aggravated disease against severe SARS-CoV-2 or acute COVID-19 infection are associated with bronchitis difficulty due to bronchial thrombosis, viral pneumonia with virus spreading and inflammation, and thrombus formation and growth by blood coagulation. The recently global COVID-19 and the coronavirus variant RNA (SARS-CoV-2 RNA mutation) pandemics have been needed as an urgent search for effective medical scientific improvements, in which the risk of severe infectious SARS-CoV-2 and the RNA mutation increases with pulmonary blood thromboembolism in respiratory COVID-19 disease and the infectious infant diseases increase, including being associated with lower zinc status. Thus, these difficulties must be overcome by the development of the medical and scientific theory and the many efforts. SARS-CoV-2 virus and the clinical disease COVID-19 in children are characteristic that minor contributors to virus transmission and differential expression of ACE2 in children which may attenuate viral entry, and host-virus factors that underpin the unique aspects of SARS-CoV-2 pathogenicity in children [1]. Children with SARS-CoV-2 infection have less severe coronaviruses disease-19 (COVID-19) than adults [2]. However, when children become have acute COVID-19 under the pandemonium, children with comorbidities have a higher risk of severe COVID-19 than children without underlying disease, in which childhood obesity is likely positively correlated with COVID-19 severity that pediatric underlying conditions play in COVID-19 severity [3]. Pediatric patients with COVID-19 infection are shown that the infected children had coinfecition with other common respiratory pathogens and the pediatric patients have prolonged fecal shedding of SARS-CoV-2 RNA during the convalescent phase that most pediatric patients had relatively mild disease with good prognosis, which could be seen in children infected with SARS-CoV respiratory viruses with innate immunity in response to pathogen [4]. COVID-19 in children is relatively mild that it is easy to miss the diagnosis in the early stages when present with a non-respiratory disease. The other, severe COVID-19 can also occur in children with underlying or coexisting diseases that the possibility of SARS-CoV-2 infection should be suspected when children show digestive tract symptoms, especially with a severe systemic inflammatory reaction and organ fever [5]. Pediatric cases of COVID-19 caused by severe acute respiratory syndrome coronavirus 2 are relatively fewer cases of COVID-19 among children compared to cases among adult patients. The mild disease in children may be related to trained immunity that refers to the use of certain vaccines [6]. On the case of severe pediatric COVID-19 pandemic infection, severe thrombocytopenia and acute respiratory distress syndrome (ARDS) are presented, including patient’s severe disease course was associated with thrombocytopenia and elevated inflammatory markers. Finally, randomized placebo controlled clinical trials was used to study drugs like tocilizumab and remdesivir to include children in addition to adults with COVID-19, in which this COVID-19 thrombus inhibition in inflammatory and respiratory ailment has been becoming recently important matters in SARS-CoV-2 infectious pandemonium [7].

On the other hand, zinc utilization to pediatric antivirus activity becomes effective for children health that zinc-binding proteins such as the metallothioneins may possess antiviral roles [8]. Zinc is an antioxidant that protects cells from the damaging effects of oxygen radicals generated during immune activation. The adverse effects of zinc deficiency on the immune system are likely to increase the susceptibility of children and lead to a zinc-deficient state. Therefore, zinc supplementation could conceivably modulate the immune and inflammatory responses to viruses in a way that are beneficial to the host [9]. The demonstrated preventive therapeutic effect of zinc in treatment of childhood pneumonia is conflicting that Zn supplementation in 2~24 months old children with radiologically verified pneumonia did not result in significant improvement of risk reduction of treatment failure. Moreover, Zn supplementation in Zn-deficient children with pneumonia until achievement of normal serum Zn levels did not improve clinical appearance of the disease [10].

In this mini-review, zinc-immune pediatric anti-viral activity for SARS-CoV-2 prevention, COVID-19 defenses of severe respiratory ailment and acute pneumonia and zinc induced anti-thrombus formation in children are discussed during ROS generation and oxidative stress in COVID-19 infection, including with Zn-binding molecular mechanism which Zn2+ ions could bind with COVID-19 RNA viral surface numerous proteins and coagulated thrombus proteins by Zn2+-centered tetrahedrally coordination pattern.
2.1. Zinc-Induced Immune Children

Zinc intakes by zinc induced immunity are known to be required 3 mg/day for 7 month to 3 years, 5 mg/day for 4~8 years, and 8 mg/day for 9~13 years in children. Zinc deficiency was very mild (3 to 5.0 mg Zn intake during the zinc-restricted period), the plasma zinc concentration remained more or less within the normal range and it decreased only after 4~5 months of zinc restriction. The other, zinc concentrations in lymphocytes, granulocytes, and platelets decreased within 8~12 weeks, suggesting that the assay of cellular zinc provided a more sensitive criterion for diagnosing mild deficiency of zinc, in which zinc enhances the upregulation of mRNA, which in both young adults and elderly subjects, zinc supplementation decreased oxidative stress markers and generation of inflammatory cytokines [11]. A range of zinc supplementation has been assessed, from 15 mg to 140 mg/week, with the upper range exceeding the Recommended Daily Intake (RDI) for children of 2 mg/day for children less than one year of age and up to 7 mg/day for children between 1 to 3 years [12].

In addition, as the minor receptors for children may cause low risk against severe COVID-19 infection, the ACE2 for children is involved that ACE2 is particularly within the lung microenvironment, where ACE2 levels are intrinsically elevated that SARS-CoV-2 host cell entry plays an integral role in the endothelial inflammatory response and the need to enforce physical distances in children with existing evidence for the role of children in the transmission of SARS-CoV-2. It has become apparent that relatively low SARS-CoV-2 morbidity and mortality seen in children, differences in ACE 2 distribution that potentially limits viral entry and subsequent inflammation and tissue injury, the role of children in virus transmission, and host-virus factors that underpin the unique aspects of SARS-CoV-2 pathogenicity in children [13].

2.2. Zinc-Immune Pediatric Prevention For Respiratory Function And Pneumonia Against 2019-Ncov Infection

Zn supplementation significantly decreased the incidence of Acute Lower Respiratory Infection (ALRI) defined according to specific clinical criteria in children aged <5 years that zinc reduced childhood with ALRI, but the effect was null if lower specificity case definitions were applied [14]. However, the factor was remained unexplained. Zinc induced pediatric preventing respiratory 2019-nCoV is required as supplementation with 10 mg zinc gluconate in Zn deficient children resulted in a nearly twofold reduction of the number of episodes of acute lower respiratory infections as well as the time to recovery [15].

Among pediatric populations zinc supplementation for more than 3 months could be effective in preventing pneumonia in children younger than 5 years of age, although the evidence was not robust enough to advocate prophylactic properties if given for shorter periods of time [16]. Given the rising burden of child mortality due to respiratory infections, particularly pneumonia and considering its decreasing impact with zinc supplementation, further reviews should be considered in which the effectiveness of zinc supplementation should be assessed for acute pneumonia provided that cases are well-defined by strict clinical criteria. Thus, zinc supplementation in children is associated with a reduction in the incidence and prevalence of pneumonia [17].

Preventing pneumonia is required that zinc supplementation alone (10 to 20 mg), for more than 3 months, was associated with a significant reduction in the rate of pneumonia by 19%, with Risk Ratio (RR) of 0.81 (95% CI 0.73 to 0.90). Mortality was not statistically different (RR = 0.85; 95% CI 0.65 to 1.11) [18].

2.3. Antiviral Activity Of Zn2+ Ions For The Children With Severe Respiratory COVID-19 Infection

Zn supplementation of 30 mg/day in Thai children reduced significantly severity of acute lower respiratory tract infections resulting in faster disease cessation and shorter hospital stay [19]. A decrease of 15% (0.78-0.94) in days and 12% (0.78-0.94) in duration of episode in acute respiratory infections was observed. Incidence of acute lower respiratory infections decreased by 62% (0.26-0.36) and the effect remained for full five months of follow up. Prophylactic zinc supplementation for two weeks may reduce the morbidity due to acute lower respiratory infections but not overall rate of acute respiratory infections in infants aged 6~11 months in similar populations [20]. Effectiveness of zinc gluconate supplementation for 2 months period compared to placebo in reducing respiratory morbidity in acute lower respiratory infected children up to 5 years of age living in zinc poor population. Zinc supplement may result in significant reduction in respiratory morbidity among children with acute lower respiratory infections [15]. Serum zinc level was very low (25.19 ± 15.49 μgmol/L) with Acute Respiratory Infection (ARI) children as compared that (55.51 ±31.15 μgmol/L) with non-ARI children, in which environment and nutritional status were found to be prevalently associated with higher incidence of acute respiratory infections and serum zinc content had been varied with corresponding sociodemographic, nutritional and health care profile [21].

2.4. Antiviral Activity Of Zn2+ Ions For The Children With COVID-19 Acute Pneumonia

Pneumonia is one of the most common implications of lower respiratory tract involvement that is inflammation on pulmonary parenchyma resulting in exudative solidification of pulmonary tissue of the effect of zinc on the clinical course of pneumonia in 3 to 60-month-old children hospitalized in pediatric wards. Adjuvant treatment with 20 mg zinc per day accelerates recovery from severe pneumonia in children and could help reduce antimicrobial resistance by decreasing multiple antibiotic exposures and lessen complications and deaths where second line drugs are unavailable. The mean reduction is equivalent to 1 hospital day for both severe pneumonia and time in hospital. All effects were greater
when children with wheezing were omitted from the analysis. 20 mg zinc per day can accelerate the recovery from severe pneumonia in children [22].

The effect of zinc on clinical course of 3 to 60-month children hospitalized due to pneumonia was assumed that this element was effective in resolving clinical symptoms and duration of hospitalization. Zinc supplements given during an acute episode are not beneficial in short-term clinical recovery from severe pneumonia in hospitalized children. Primary outcome was recovery from pneumonia which included the incidence and resolving clinical symptoms and duration of hospitalization [23]. Zinc may have improved their nutritional status, specially 30 mg/day of zinc supplementation reduces pneumonia in children with Chronic Kidney Disease (CKD) [24]. Zinc supplementation + ChloroQuine (CQ)/ Hydroxy ChloroQuine (HCQ) may be more effective in reducing COVID-19 morbidity and mortality than CQ or HCQ in mono-therapy [25].

The serum zinc level returned to a normal level (median, 53.20 μmol/L) on day 12 ± 2 in the treatment. There was no statistical difference in the pediatric critic illness score, lung injury score, length of hospital stay and duration of mechanical ventilation between the zinc treatments[26]. The mean serum zinc in patients was normal (80.77 ± 25.3 μg/dL) yet, the mean serum zinc level in Pediatric Intensive Care Unit (PICU) patients was lower than that of general ward patients that the lower the serum zinc level, the higher the grade of respiratory distress among children with pneumonia [27]. Zinc sulfate plus hydroxy chloroquine may play a role in therapeutic management for COVID-19 without PICU [28].

2.5. Zinc-Induced Anti-Thrombus Formation In Children

Zinc can prevent COVID-19 thrombosis that the contribution of extracellular or intracellular Zn2+ to megakaryocyte and platelet function and dysregulated Zn2+ homeostasis in platelet-related diseases by focusing on thrombosis, ischemic stroke and storage pool diseases. Consequently, zinc ions can impair the coagulation pathway and fibrin clot formation in humans, which can be more critical in patients with combined defects of both α and δ-granules or with thrombocytopenia [29]. For anticoagulation therapy in COVID-19 patients with children and adolescent below 18 years, the anticoagulation chemoprophylaxis with enoxaparin for patients with moderate, severe, and critical COVID-19 are indicated critically ill, intensified anticoagulation with therapeutic dose [30]. Venous Thromboembolism (VTE) is rare in children and the intracardiac thrombus formation has rarely been described in the COVID-19 patients that indicate higher thrombotic risk in COVID-19 patients, in which there are hypercoagulation and acute thrombosis in patients with COVID-19 infection. Hence, conservative treatment with anticoagulation should be indicated in order to prevent subsequent hypercoagulation and thrombus formation [31].

COVID-19 is associated with hypercoagulability and Disseminated Intravascular Coagulation (DIC). Children infected with SARS-CoV-2, with noted elevations in D-dimer and Maximum Clot Firmness (MCF) on Rotational Thromboelastometry (ROTEM), indicating hypercoagulability that ROTEM testing is feasible and recommend that its utility in determining the hypercoagulable state merits further study in children, who have shown can exhibit clinical severity and laboratory evidence of a coagulopathy identical to that seen in adults with SARS-CoV-2 [32]. This Thrombotic Microangiopathy (TMA) in children with SARS-CoV-2 has been observed that a high proportion of tested children with SARS-CoV-2 infection had evidence of complement activation and met clinical and diagnostic criteria for complement-mediated TMA [33]. These thromboses of the coagulopathy by hypercoagulation and the microangiopathy may be anticipated to be inhibited by zinc ions that zinc(10-20 mg daily) could modulate hypercoagulation and subsequent COVID-19 thrombus formation [10]. Zinc itself (1 to 3 m mol/L) induces platelet aggregation and augments aggregation induced by other agonists strengthens the view that zinc may play an important role in hemostasis, thrombosis and atherosclerosis [34]. Thus, zinc ions may prevent COVID-19 thrombus formation and inhibit the thrombus growth for children with COVID-19 patients, causing that zinc-induced decreasing platelet count modulates the activity of coagulation protein [35].

2.6. Zinc-Induced ROS Generation In COVID-19 Bronchitis, Pneumonia, And Thrombosis

Respiratory viruses are known to induce Reactive Oxygen Species (ROS)-generating enzymes, including nicotinamide adenine dinucleotide phosphate oxidases (NADPH oxidases, Nox) and Xanthine Oxidase (XO) to disturb antioxidant defenses. ROS generation can induce cell death and the release of virions representing possible proviral role of enhanced ROS production and altered redox balance. The oxidative stress is the triggering of an antiviral immune response. too strong immune responses lead to a cytokine storm and severe inflammation, which is very dangerous for tissue and may disturb lung function. Antioxidant supplementation is expected to ameliorate the consequences of infection [36].

Zinc induced ROS generation in respiratory and pulmonary COVID-19 infected cells is that the univalent reduction of oxygen generates superoxide (•O2−), hydrogen peroxide (H2O2), and hydroxyl radicals (•OH). Superoxide has an unpaired electron, which imparts higher reactivity and renders it very unstable and short-lived. A disequilibrium between ROS generation and elimination by the antioxidant defense system results in increased bio-availability of ROS, leading to an oxidative stress. Inflammation-induced oxidative stress from injured cells could lead to irreversible cellular or tissue damage with the passage of time [37]. Thus, zinc acts as a potent agent by inhibition of ROS production and inflammation. The oxidative stress in pediatric diseases causes an
oxidative burst that result in a respiratory burst and rapid ROS production, including superoxide and hydrogen peroxide [38]. However, ROS production in zinc(II)-immune pediatric patient with COVID-19 bronchitis and pneumonia cannot be elucidated yet. ROS resolve venous thrombus in children that Deep Venous Thrombus (DVT) formation and resolution are influenced by ROS through modulation of the coagulation, fibrinolysis, proteolysis and the complement system, and ROS induce tissue damage, thrombosis and Red Blood Cell (RBC) dysfunction, which contribute to COVID-19 disease severity [39]. The development of novel antioxidant treatments that aim to abrogate the formation of DVT or promote its resolution will depend on the ROS within the RBC oxidative stress, which can affect major processes involved in the development of venous thrombosis of RBC ROS in the activation of thrombotic events [40].

In addition, the role of zinc to pediatric vaccine plays an important 2019-nCoV RNA viral degradation, whether a transcriptional step may be involved in zinc-caused inhibition of vaccine virus growth, zinc-ions at lower concentration could inhibit the infection by viral mRNAs degradation, and zinc-ions could inhibit 2019-nCoV by recruiting both the 5’ and 3’ mRNA degradation to specifically promote the degradation [41], including that recently 2019-nCoV RNA mutation could be inhibited by using Zn2+ ions-binding coordination pattern.

Zinc pediatric intake may be required to be effective range 10−20 mg/d for 2019-CoV prevention, 10−30 mg/d for reduction of COVID-19 bronchitis, and 10−30 mg/d for anti-thrombus formation and growth, in which the molecular mechanism may possess that Zn2+ ions could bind with viral surface proteins and thrombosis protein by Zn2+-centered tetrahedrally coordination pattern [42]. Thus, Zn2+-induced pediatric anti-respiratory activity is enhanced and provided direct protective effects with using zinc gluconate 10 mg, zinc supplementation 30 mg/day, and zinc 15 mg~30 mg daily with lozenges, Zn2+-induced pediatric anti-pulmonary activity is enhanced for Adjuvant treatment with 20 mg zinc/day, 30 mg/day of zinc supplementation with CKD. Furthermore, Zn2+-induced pediatric anti-thrombotic activity is enhanced that zinc ions (Zinc 10~30 mg/day) could modulate coagulopathy by hypercoagulation and the microangiopathy, Zn2+ induced platelet-dependent fibrin formation lead to modulation of thrombus formation, Zn2+-induced platelet activation enhances anti-thrombus growth, and ROS resolve venous thrombus.

### 2.6. Zinc Ions-Binding Protein Molecular Mechanism

Zinc(II) ions-induced immune antiviral molecular mechanism may be caused that Zn2+ ions are bound with COVID-19 proteins molecules, such as S (spike), E (envelope), M (membrane) and N (nucleocapsid) proteins of envelope virus COVID-19 [43] by zinc ion coordinated tetrahedrally or Zn2+ triad binding structure formation, leading to the formation of zinc coordinated binding proteins molecules. Further, Zn2+ ions-induced anti-thrombus formation and growth molecular mechanism may be resulted that Zn2+ could bind with coagulated protein (thrombus protein) by Zn2+ ions-centered tetrahedrally coordination pattern [44].

As mentioned above, Zn2+ ions-induced pediatric anti-viral activities for respiratory and pulmonary organs, and anti-thrombus formation during ROS generation against severe COVID-19 infection, and the zinc binding proteins molecular mechanism, are represented in (Table 1).

| Table 1: Zn2+ ions-induced pediatric anti-respiratory, anti-pulmonary, and anti-thrombotic activities during ROS generation against severe COVID-19 infection, and the zinc binding protein molecular mechanism |
|---|---|---|---|---|
| Zn2+ ions | Zn2+-induced pediatric anti-viral activity for respiratory and pulmonary organs, and anti-thrombus formation during ROS generation against COVID-19, and its zinc(II) binding proteins molecular mechanism |
| Zn2+ | Prevention | Anti-Respiratory Infection | Anti-Inflammatory Pneumonia | Anti-Thrombus Formation and Growth |
| → Zn2+ | •Zn homeostatic immune conc 3~8 mg/day from 7 month, 3 year to 13 years ages | → Zn2+, (•O2+, H2O2, •OH) | → Zn2+, (•O2+, H2O2, •OH) | → Zn2+, ROS |
| •Zinc supplementation in combination with CQ/HCQ | •Zinc gluconate 10mg in acute lower respiratory infection | •Adjuvant treatment with 20 mg zinc per day Normal (80.77 + 25.3 μg/dL) | •Adjuvant Zinc Therapy on children | •Zn2+-induced platelet-dependent fibrin formation lead to modulation of thrombus formation. |
| •Routine zinc supplement prevents acute lower respiratory infection | •Zn supplementation (30 mg/day) in Thai children | •Adjuvant Zinc Therapy on Pneumonia Recovery from Pneumonia | •Lower the serum zinc level, higher the grade of |
| •Pediatric preventing respiratory 2019-nCoV supplementation in infants aged 6 ~ 11 months | •Prophylactic zinc | •Zn2+-induced platelet activation enhances anti- | |

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### 3. Conclusion

Zinc(II)-immune pediatric anti-viral activities for SARS-CoV-2 prevention and COVID-19 defenses of bronchitis and pneumonia and Zn²⁺ ions-induced anti-thrombus formation during ROS generation are discussed, and these Zn²⁺-dependent pediatric veridical activity effects and anti-thrombus formation result in the following.

Zinc induced pediatric preventing respiratory 2019-nCoV is provided that specifically, supplementation with 10 mg zinc gluconate in Zn deficient children resulted in a nearly twofold reduction of the number of episodes of acute lower respiratory infections as well as the time to recovery. Zinc supplementation in children is associated with a reduction in the incidence and prevalence of pneumonia.

Preventing pneumonia is required that zinc supplementation alone (10 to 20 mg), for more than 3 months, was associated with a significant reduction in the rate of pneumonia by 19%, with an RR of 0.81 (95% CI 0.73 to 0.90). Supplementation (30 mg/day) in Thai children significantly reduced severity of acute lower respiratory tract infections resulting in faster disease cessation and shorter hospital stay. Prophylactic zinc supplementation for two weeks may reduce the morbidity due to acute lower respiratory infections but not overall rate of acute respiratory infections in infants aged 6–11 months in similar populations. Zinc gluconate supplementation may result in significant reduction in respiratory morbidity among children with acute lower respiratory infections in zinc poor population.

Zinc deficiency was very mild (3 to 5.0 mg Zn intake during the zinc-restricted period), the plasma zinc concentration remained more or less within the normal range and it decreased only after 4~5 months of zinc restriction. The other, zinc concentrations in lymphocytes, granulocytes, and platelets decreased within 8~12 weeks, suggesting that the assay of cellular zinc provided a more sensitive criterion for diagnosing mild deficiency of zinc, in which zinc enhances the upregulation of mRNA, which in both young adults and elderly subjects, zinc supplementation decreased oxidative stress and generation of inflammatory cytokines.

Zinc intakes by zinc induced immunity are required 3 mg/day for 7 month to 3 years, 5 mg/day for 4~8 years, and 8 mg/day for 9~13 years in children. Supplementation have also been assessed, from 15 mg to 140 mg/week, with the upper range exceeding the RDI for children of 2 mg/day for children less than one year of age and up to 7 mg/day for children between 1 to 3 years.

Thus, Zn²⁺-induced pediatric anti-respiratory activity is enhanced and provided direct protective effects with using zinc gluconate 10 mg, zinc supplementation 30 mg/day, and zinc 15 mg~30 mg daily with lozenges, Zn²⁺-induced pediatric anti-pulmonary activity is enhanced for adjuvant 20 mg zinc/day, 30 mg/day of zinc supplementation with CKD.

Pneumonia is an inflammation on pulmonary parenchyma resulting in exudative solidification of pulmonary tissue, having the effect of zinc on the clinical course of pneumonia in 3 to 60-month-old children hospitalized in pediatric wards. Adjuvant treatment with 20 mg zinc per day accelerates recovery from severe pneumonia in children. 30 mg/day of zinc supplementation reduces pneumonia in children with CKD. Zinc + CQ/HCQ may be more effective in reducing COVID-19 morbidity and mortality.

The thrombosis of the coagulopathy by hypercoagulation and the microangiopathy may be anticipated to be inhibited by zinc ions that zinc(10~20 mg daily) could modulate hypercoagulation and subsequent COVID-19 thrombus formation. Zinc of 1 to 3 mg mol/L induces platelet aggregation and augments aggregation in-
duced by other agonists strengthens the view that zinc may play an important role in hemostasis, thrombosis and atherosclerosis. Thus, as zinc ions modulate the activity of protein of coagulation, zinc ions may prevent COVID-19 thrombus formation and inhibit the thrombus growth for children with COVID-19 patients.

Furthermore, \( \text{Zn}^{2+} \)-induced pediatric anti-thrombotic activity is enhanced that zinc ions (Zinc 10~30 mg/day) could modulate coagulopathy by hypercoagulation and the microangiopathy, \( \text{Zn}^{2+} \)-induced platelet-dependent fibrin formation lead to modulation of thrombus formation, \( \text{Zn}^{2+} \)-induced platelet activation enhances anti-thrombus growth, and ROS resolve venous thrombus.

Accordingly, zinc pediatric intake may be required to be effective range 10~20 mg/d for 2019-CoV prevention, 10~30 mg/d for reduction of COVID-19 bronchitis, 20~30 mg/d for recovery from COVID-19 pneumonia, and 10~30 mg/d for anti-thrombus formation and growth.

Zinc induced ROS generation and oxidative stress in COVID-19 bronchitis, pneumonia, and thrombosis in children that are caused by mRNA degradation and oxidative respiratory burst, and thrombosis revoluted by tissue damage. Respiratory viruses are known to induce ROS-generating enzymes and lead to an oxidative stress that the oxidative stress in pediatric diseases causes an oxidative burst those results in a respiratory burst and rapid ROS production, including superoxide and hydrogen peroxide.

Zinc(II) ions-induced immune antiviral molecular mechanism may be caused that \( \text{Zn}^{2+} \) ions are bound with COVID-19 proteins molecules such as S (spike), E (envelope), M (membrane), and N(nucleocapsid) proteins of envelope virus COVID-19, leading to the formation of zinc ions-coordinated binding proteins molecules. Further, \( \text{Zn}^{2+} \) ions-induced anti-thrombus formation molecular mechanism is involved that \( \text{Zn}^{2+} \) may be bound with coagulated thrombus protein by \( \text{Zn}^{2+} \)-centered tetrahedrally coordinated pattern.

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